INTRAMOLECULAR ISOTOPE EFFECTS FOR THE STUDY OF REACTIONS WITH MASS TRANSFER LIMITATIONS

A Thesis

by

JOSHUA G. WAGNER

Submitted to the Office of Graduate Studies of
Texas A&M University
in partial fulfillment of the requirements for the degree of

MASTER OF SCIENCE

May 2009

Major Subject: Chemistry

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Approved by:

Chair of Committee,	Daniel Singleton
Committee Members,	Coran Watanabe
	Pingwei Li
Head of Department,	David H. Russell

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ABSTRACT

Intramolecular Isotope Effects for the Study of Reactions With Mass Transfer Limitations.

(May 2009)

Joshua G. Wagner, B.S., Villa Julie College

Chair of Advisory Committee: Dr. Daniel Singleton

The research presented provides a method to use the comparison of intermolecular isotope effects vs. the intramolecular isotope effects for the study of reactions in which study of the rate limiting step is ambiguous due to interfering mass transfer effects. The oxidation of unfunctionalized hydrocarbons at mild conditions developed by Sir Derek Barton, the Gif reaction is the model used. The history is provided to demonstrate the relevance of using this model as one which could show the usefulness of this method. Evidence has been provided and used to theorize that the rate limiting step of the reaction may be diffusion of the reactants, not a chemical change. Starting materials were made which would allow for the measurement for both the intermolecular and intramolecular KIE and those values were compared. The results show that there is little difference between the intermolecular and intramolecular KIE, therefore the reaction is not diffusion controlled.

ACKNOWLEDGEMENTS

I would like to acknowledge many on my road here. It has been a long one but I would like to thank first my advisor, Dr. Dan Singleton, who has shown tremendous patience and support. I would also like to thank my committee members, Dr. Coran Wantanabe and Dr. Pingwei Li. Finally I would like to thank my wife who began this process with me before we were married and supported me throughout. Thanks all.

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CHAPTER I

INTRODUCTION: THE ISOTOPE EFFECT

Mechanistic studies have been vital in the advancement of organic chemistry. With knowledge of the mechanism it is possible to design new reactions in a rational fashion or expand an existing reaction methodology. While many great have been made by accident a chemist would have much advantage to have mechanistic knowledge of a reaction.

There are many ways to study mechanism. A chemist may study the steric effects of a reaction, and thereby gain insight on the mechanism, by studying the relative reactivity of different substituted substrates. Comparing rates of reaction in different solvents can give insight into intermediate states in a mechanism. Hammett plots are a powerful way to look at the electronic demands of a reaction. Trapping agents may help to prove the existence of certain intermediates as well. One of the most powerful tools that chemists have is the kinetic isotope effect (KIE).

Theory

KIE's are very powerful tools that physical organic chemists have access to and can yield much insight into the mechanism and transition state of a reaction. This is because the KIE results from bonding changes that occur in the rate determining transition state

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This thesis follows the style of *Journal of American Chemical Society*.

of a reaction. However, careful interpretation as well as a clear understanding of the origin of the KIE is crucial to gaining the full amount of information from a given set of KIE's.

A KIE arises from the difference in rate of the reaction of different isotopomers. This can be observed as the different concentrations of products arising from the reaction of

$$\frac{k_H}{k_D} = \frac{[H_{prod}]}{[D_{prod}]} \qquad \text{Equation (1)}$$

the different isotopes and can be represented by Eq. (1) In this way measurement of the KIE in many cases is rather simple and can be done with a ^{1}H NMR, but does however typically entail the labor intensive and expensive synthesizing of labeled materials.

The next question then is what causes the different isotopes to react at different rates. Very important to note is that the substitution of one isotope for another does not change the potential energy surface so the reaction is essentially the same sterically and electronically. The difference comes from the mass of the reacting isotopes and how it changes the zero point energy of the reacting bonds. In other words the bond energy being the sum of the energy from the zero point to the point of break the heavier isotopomer has a stronger bond because while the surface remains the same the bottom of the energy well is lower resulting in a larger change in energy to break the bond. This will be expanded upon more in Chapter III.

Understanding the difference between inter and intramolecular KIE's is imperative to understanding how these might be used. Intermolecular KIE's arise from comparison of deuterium to hydrogen between two separate molecules whose difference is the substitution of isotopomers. Intramolecular KIE's arise from rate comparisons of two equivalent positions on a single molecule one of which has deuterium and the other which has hydrogen. The distinction will become further clarified as it is further explained in Chapter III.

The proposed work is to develop a new way to use the kinetic isotope effect as a tool to probe the mechanisms of reactions. This will involve the comparison of the intra-molecular isotope effect to the intermolecular isotope effect. Using this will allow a probe of the involvement of mass transfer steps which happen in between the chemical steps. The kinetic isotope effect is so useful because it can directly represent what is going on in a reaction during a rate limiting transition state. The limitation of this tool is that it is only effective for the transition state of the rate limiting step of a reaction. If a mass transfer step is the highest barrier in a reaction coordinate it now the rate limiting step and the kinetic isotope effect gives no information on the transition state of the chemical transformations occurring.

While it may not seem like it occurs very often this actually is a common issue when studying reaction mechanisms in enzyme catalysis. Enzymes are often lower the barrier

energy of the reaction they are designed to catalyze the limitation of the reaction is the rate at which the substrates come into the active site of the enzyme.

In the case of the intermolecular isotope effect the whole reaction coordinate is involved and the effect of the difference of the rate of reaction of two different isotopes in the chemically important transition state is diluted by the fact that the overall rate is limited by how fast the active species involved come together. The intramolecular isotope effect erases this effect because every time there is contact between active species the choice between isotopes is presented for the chemically important transition state.

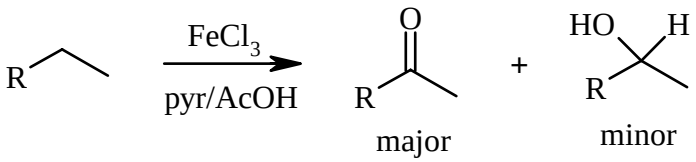
CHAPTER II

THE GIF REACTION

Background

The Gif reaction is a very controversial reaction which was introduced by Sir Derek Barton. It involves the oxidation of alkanes to ketones, using a simple iron salt in pyridine/acetic acid solvent as shown in the scheme along with an oxidant such as SO_2, H_2O_2, O_2, or tert-butly hydroperoxide(*t*-BuOOH).

Scheme 1.



Over the years a whole family of oxidation reactions were developed all being similar and falling under the general Gif reaction. Table 1 below lists the different Gif reactions in chronological order. The names listed are derived from where the research on the particular reaction was developed. In this paper the reaction will generically be referred to as the Gif reaction unless an explicit reaction needs to be specified. Also to note the table those Gif conditions utilizing *t*-BuOOH, however these conditions were acknowledged by Barton as being radical and were discarded from the Gif family[1].

Table 1. The family of Gif chemistries.

Name	*Precatalyst*	*Oxidant*	*reductant*	*Solvent*
GifI	*Metallic iron powder*	*O2*	*SO2*	*Pyr/AcOH*
GifII	*Metallic iron powder*	*O2*	*SO2*	*Pyr/AcOH*
GifIIII	*Metallic iron powder*	*O2*	*SO2*	*Pyr/AcOH*
GifIV	*FeII/III*	*O2*	*Zn*	*Pyr/AcOH*
GO	*FeII/III*	*O2*		*Pyr/AcOH*
GoAggI	*FeII*	*KO2*		*Pyr/AcOH*
GoAggII	*FeIII*	*H2O2*		*Pyr/AcOH*
GoAggIII	*FeIII/Picolinic acid*	*H2O2*		*Pyr/AcOH*
GoChAggI	*CuII*	*H2O2*		*Pyr/AcOH*
FamGoChAggII	*Metallic iron powder*	*O2*		*Pyr/AcOH*
GoAggIV	*FeIII*	*t-BuOOH*		*Pyr/AcOH*
GoAggV	*FeIII/Picolinic acid*	*t-BuOOH*		*Pyr/AcOH*

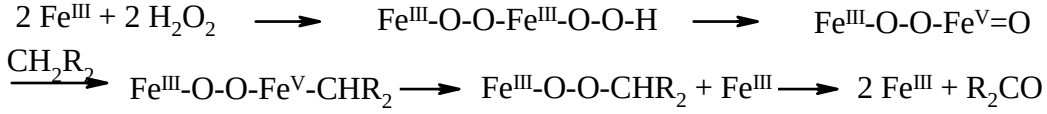
The origin of Gif chemistry comes from trying to mimic natural catalysts. There are several enzymes such as Cytochrome P450 and MMO which are able to oxidize hydrocarbons to alcohols. These enzymes hold metal centers in configurations using amino ligands which are able to perform oxidation chemistry very readily. The pyridine in this case is nitrogen containing compound which is meant to somewhat mimic the amino ligands in the enzyme and allow for a mimic of the enzyme. The first generations of this chemistry worked somewhat well and succeeding generations were improvements. Later generations also included ligands such as picolinic acid to more closely mimic the enzyme active sites.

This type of reaction is of high importance in industry as most of the basic starting materials for making chemicals come in the form of unoxidised alkanes. This being the

type of compounds that are normally found in the crude oil that comes out of the ground or the first generation products arising from the initial separations of crude Carbon hydrogen bonds are very strong and are in general very difficult to oxidize with high conversion and selectivity. In relative terms the Gif chemistry had high selectivity and conversion at low temperatures and pressures allowing for the possible use. This could be loosely compared to the oxidation process of butane by Cobalt catalyst at high temperature and pressure to produce acetic acid. The process has low selectivity and the process uses a large number of energy intensive distillations to purify out the other products produced.

Other similar reactions exist which were generally believed to be radical in nature such as Fenton chemistry which is an iron metal mediated oxidation similar to Gif chemistry. However Barton because of some novel selectivity, which will be elaborated on more later, he proposed that the reaction which he introduced was a C-H bond insertion by an iron superoxide species with an overall reaction mechanism as illustrated in Scheme 2.

Scheme 2.



Having a model mechanism gives a good starting point in optimizing the conditions of a reaction. Such a model also helps in the application of a reaction to other possible substrates or any other change that a researcher may want to make. This is ultimately a more efficient method of research than going about such things blindly.

The non-radical reaction mechanism that Barton proposed as was presented above did not go uncontested. Several other chemists have contended that the mechanism is in fact a radical one. Much of this is because the proposed Fe^{V} superoxide is difficult to accept. Many believe that the simplest answer is often the correct one and the Fe^{V} superoxide is not the simplest explanation.

Barton does not make the claims of a non-radical mechanism without any evidence to support that claim, the first peculiarity which Barton noticed was the selectivity of the reaction products. Most radical reaction give high tertiary to secondary selectivity but when he performed reaction with adamantane as substrate he noticed the products of his Gif chemistry favored oxidizing the secondary position to give a secondary to tertiary (which is denoted C_2/C_3) ratio of 5.7-22 depending on the Gif conditions used. Using benzoyl peroxide as an oxidant on adamantane as a known radical process he got a ratio of .8 which led him to believe that the mechanism was in fact different and must be a non-radical mechanism[2].

The above evidence was one of the most hotly debated pieces of the puzzle and after much study by Barton and other chemists the issue turned out to be more complex than simply this. The first complexity was pointed out by Barton himself [3] in which he pointed out that oxidized product were not the only ones formed but also present were pyridine coupled products as well, which would be formed by a radical mechanism, however he finds pyridine coupled only to the tertiary position of the adamantane and

rationalized this as the tertiarty iron carbon bond on the intermediate is weak enough to rupture forming radicals. Barton also refines his C_2/C_3 to 1.15 which he purports is still beyond the range for a radical reaction and therefore still supports the non-radical mechanism. To further the difference between the radical reaction from Gif chemistry he used PTOC esters to produce authentic tertiary and secondary radicals of adamantane and compared the oxygenated products to the pyridine coupled products and found that the product distribution for the authentic radicals differed from that observed in Gif[IV].

Perkins refuted the C_2/C_3 calculated by Barton however, and calculated a value of 3 in favor of the tertiary position with this new data[4]. He has a footnote pointing out that there is some error in the previous calculation incurring with the per site calculation as opposed to the per hydrogen calculation. The tertiary position was functionalized by not only oxidation but also by alkylation with pyridine. It was once these products were included in the calculation for tertiary to secondary reactivity as well as the error in the per site versus the per hydrogen in the calculation that the secondary to tertiary ratio was shown to in fact favor the tertiary position over the secondary position. Therefore according to Perkins the C_2/C_3 is in favor of a radical process.

When acknowledged by Barton that the pyridine coupled products were present he then used the amount of alkylated products in the tertiary position being much more abundant than those in the secondary position as being in favor of a nonradical process[1]. This was in relation to control experiments where genuine alkyl radicals were formed in the

presence of pyridine and the ratio of alkylated products was equal. However this product distribution of the authentic secondary and tertiary radicals suffered from a problem according to Stavropoulos. In the control experiment the radicals were generated in pyridine without iron present. However it was shown when iron is added to the solution in which the radicals are produced, as would be the case in a Gif reaction, the product profile from the genuine radicals does indeed match that of the Gif conditions.

The relative stabilities of the cyclopentane radical vs the cyclohexane radical are different, the cyclopentane radical is more stable and a relative reactivity greater than one would be in accordance with a radical mechanism. This is proven in the Fenton reaction, known to produce hydroxyl radicals, which gives a ratio of 1.14. Barton compared the relative reactivities under Gif^{IV} conditions the relative reactivity is 60 which Barton uses as more evidence to prove the non-radical nature of the Gif reaction.[5] This evidence as was pointed out by Perkins[4] would have to be reevaluated taking into consideration the pyridine coupled products. Since this was never undertaken this evidence cannot be used.

Another modification to Gif chemistry that Barton used as evidence for the nonradical mechanism was that then trimethyl phosphite was added to the Gif^{IV} conditions the resulting unexpected product was cyclohexyl dimethyl phosphate[6]. In control experiments is was shown that the cyclohexyl hydroperoxide, the proposed intermediate for the radical reaction was reduced by the trimethyl phosphite to cyclohexanol. Missing

from the control experiment was iron. Perkins suggests that with iron present there is a perfectly reasonable radical mechanism that can be followed to get to the observed product[4]. With the iron present the cyclohexyl hydroperoxide could be decomposed to generate cyclohexyloxyl radical which could then be attacked by the phosphite and the oxidized by Fe(III) to the tetraalkyloxyphosphonium ion. This could then be attacked by a nucleophile to produce the observed product. A second control was performed in the original paper by Barton using Fe in the control experiment and the cyclohexyl dimethyl phosphate, but was neglected in the discussion.

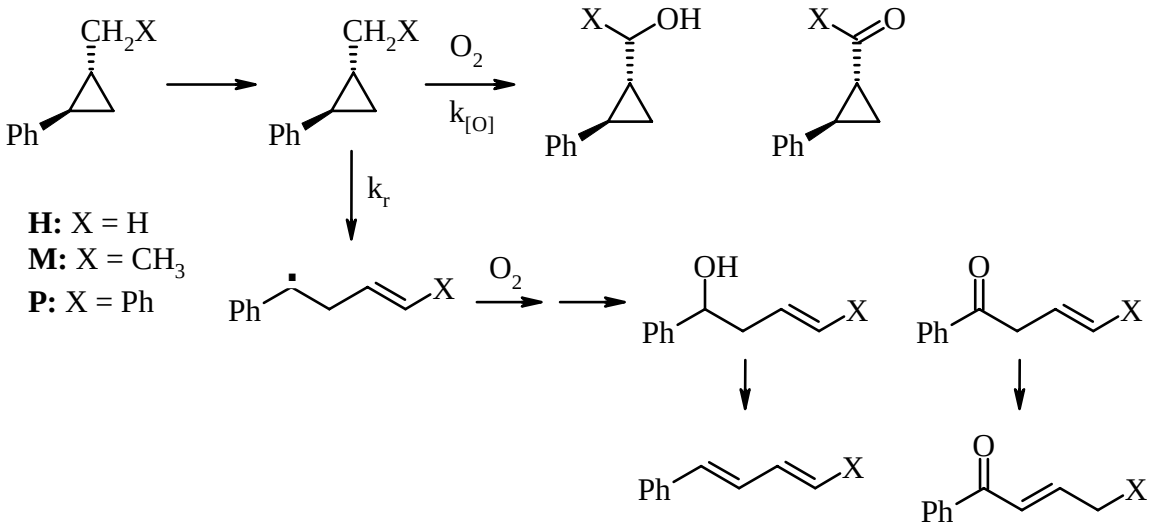
If the reaction is in fact radical then Barton reasoned that a radical trap such as PhSeH, which would reduce a carbon radical to an alkane and would surpress the reaction with only starting alkane resulting. When PhSeSePh is added to the reaction, which was believed to form PhSeH under the reaction conditions, the formation of PhSe-R is the major product.[7] This was taken as evidence that the PhSeH was capturing the the iron carbon bond after the Fe^{V} superoxide insertion into the carbon hydrogen bond.

The above has been refuted by Perkins and is complicated by a publication that Barton made with Sawyer[8]. Firstly Perkins points out that in the reaction conditions the PhSeH will actually be in the deprotonated form and therefore would be very likely to form the PhSe-R derivatives. This is in concurrence with a second in the paper with Sawyer the production of the PhSe-R derivatives are given as evidence that radicals are present in

Fenton like conditions, purportedly because in those conditions the PhSeH would be in the deprotonated form.

Newcombe has come up with a very interesting way in which to study whether a reaction goes through radical or other mechanisms.[9] By using cyclopropanes as substrate it is possible to observe the product profile one can tell if a radical mechanism. The reaction is illustrated in Scheme 3.

Scheme 3.



As in the case with non-stabilized radicals the radical reaction (k_r)will be much faster than oxidation ($k_{[O]}$) and ring opened products will dominate. By comparing the product selectivities of known radical and non-radical processes one can make a conclusion as to which process either radical or non-radical the Gif chemistry is. The product profile that one would expect to see in a radical process is one in which most of the products in the less stabilized cyclopropane rings are mostly the ring opening products with some small

amounts of intact ring oxidized products as the starting material used is the phenyl stabilized version there will be more of the closed ring oxidized products but not as much as with a true non-radical oxidation. Newcombe observed only ring opened products with the unstablized cyclopropane ring and only traces of non-ring opened products with the phenyl stabilized starting material with a product distribution very similar to a know radical reaction mechanism chemistry[9]. From this evidence he concludes that the Gif reaction is a diffusion controlled radical mechanism.

The above is only a sampling of the evidence, however it is representative. The overall consensus as shown by the strong refutes by Minisci and Perkins as well as the evidence from Newcombe. With this in mind it has only disproves that it is an insertion mechanism. The question that remains is that which was voiced by Gozzo "A fundamental question has always been the object of endless disputes: to what extent is $^{\bullet}$OH produced in the free-state and to what extent as an oxygenated metal complex?"[10] Or is Newcombe correct in his assertion that the radical is a freely diffusing one?

One piece of evidence that is very notably missing after all the discussion of using KIE's to study reaction mechanisms is that nowhere is the KIE of this reaction mentioned. In this case, and many other cases of complex multi-step reaction processes, a modest kinetic isotope effect is of little help and can sometimes be used to argue for different mechanisms.

CHAPTER III

THEORY

Isotope Effect

What is a kinetic isotope effect? Isotopes are two different molecular weight versions of the same element, and they react at different rates. So if a site that is involved in bond changes during a reaction is labeled with both the lighter and heavier isotope an observer can measure the difference in rates of reaction. This is known as the kinetic isotope effect.

While the weight of two different isotopes is different the energy surface potential remains the same. The difference in reaction rates comes from the Zero Point Energy difference between the two isotopes. The Zero Point Energy comes from

$$\nu = \frac{1}{2}\sqrt{\frac{k}{m}} \qquad \text{Equation (2)}$$

the vibrational frequency and is calculated from Eq. (2), where k is the spring force constant and is equal in both cases and m is the mass of the element in question. In the case of hydrogen this mass would be one and for deuterium the mass would be two. From this calculation the resting state Zero Point Energy can be seen to be lower for the heavier isotope. As the bond reaches the transition state the Zero Point Energy decreases and the Zero Point Energy for deuterium is nearly the same as that for hydrogen but

starts out at a lower point the bond strength for the X-D bond is stronger than the X-H bond and therefore reacts at a slower rate. This is shown graphically in Fig. 1 below.

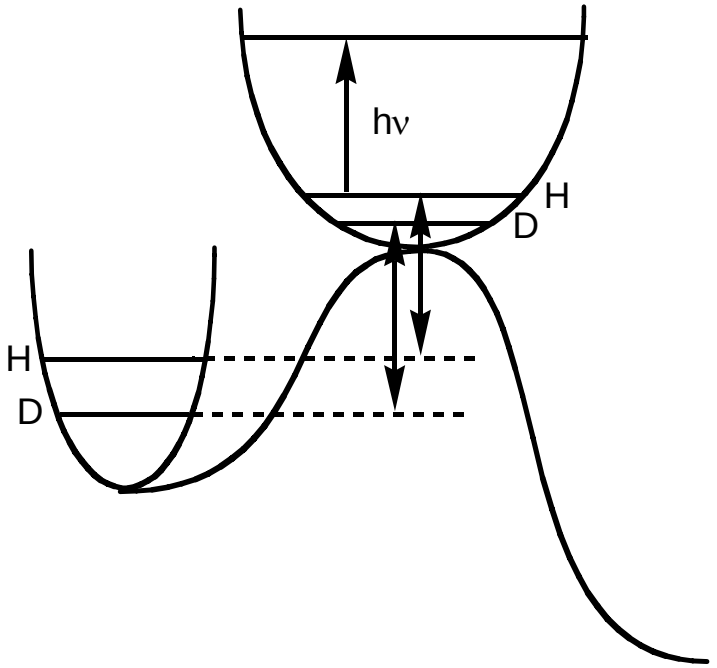


Figure 1. The origin of the kinetic isotope effect.

The example is that of hydrogen but the isotope effect will show up with any element where a heavier isotope can be substituted for another. The most common isotopes used being hydrogen, carbon, oxygen and nitrogen. The difficulty with using the elements larger than hyrdrogen lies in the fact that the relative difference between the molecular weight of the two isotopes is not as great as that of hydrogen. The molecular weight of hydrogen is 1 and the molecular weight of deuterium is 2 therefore there is a relative difference in weight of 100%. For C^{12} versus C^{13} the relative difference is 8%. This

means that the difference in the Zero Point Energy between the two will be much smaller than that for hydrogen versus deuterium.

Intermolecular Case

Let us first examine what would be occurring in the intermolecular case. A fairly well known phenomenon is that of the formation of a radical which is contained in a solvent cage. This complex would be present in a situation where a free hydroxyl radical would be solvent caged with a substrate molecule.

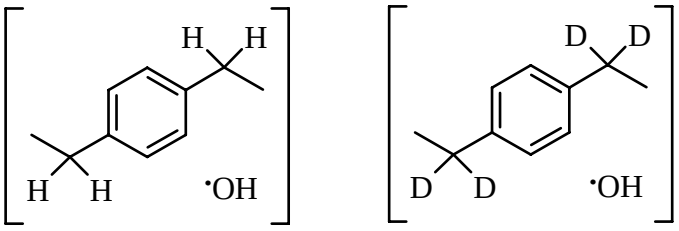


Figure 2. The solvent cage complexes of substrate and radical in intermolecular case.

In the intermolecular case the complex would be formed with either a deuterated substrate or a substrate with only protons as shown in Fig 2. Since there is an equal amount of both substrates there would be an equal amount of both complexes at any one time. Hydrogen reacting at a faster rate, however would produce more of the product deriving from the per hydrogen substrate and thereby would show a kinetic isotope effect. However is a reaction is diffusion controlled the barrier to the radical diffusing

away would take place slower than the reaction with either hydrogen or deuterium. So even if there is a difference in rate of radical hydrogen abstraction the radical would have time to react with either before diffusing away to make another alternate contact. If the reaction not limited by diffusion the radical would have time to diffuse away before reacting with the deuterium meaning there would be an accumulation of product deriving from the reaction of the radical with hydrogen.

Intramolecular Case

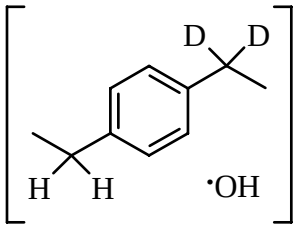


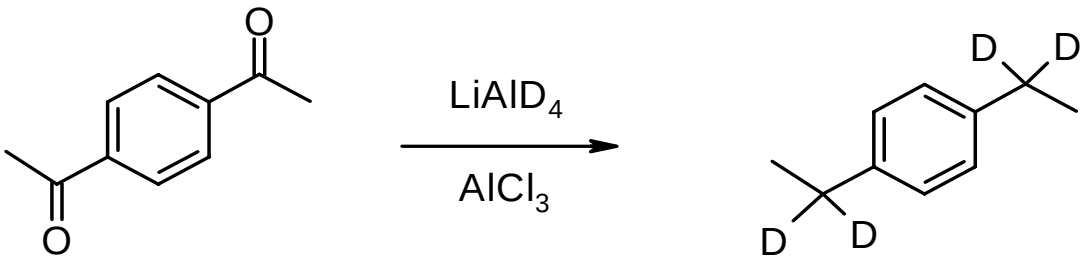
Figure 3. The solvent cage complex of substate and radical in intramolecular case.

In the intramolecular case each complex that is formed the radical has the choice between either hydrogen or deuterium as can be seen in Fig 3. In this case it would not matter if the rate of diffusion is slower than the radical hydrogen abstraction because the radical has the choice between hydrogen and deuterium from each collision, and the kinetic isotope effect would only depend on the relative rates of reaction of either the hydrogen or deuterium. If the reaction is diffusion controlled then it would be expected that the KIE for the intramolecular case would be higher since every collision would represent a choice between H and D before the radical diffuses away. Because of this

fact a comparison of the intra- versus intermolecular kinetic isotope effect could be used to determine if diffusion or otherwise mass transfer limited.

For this study there will be two different labeled compounds made to be able to calculate the isotope effect. For the intermolecular isotope effect the d_4-diethylbenzene will be made using the method shown in Scheme 4.

Scheme 4.



This will be mixed with an equal amount of the non-deuterated and version and the final concentrations of the hydrogen versus the deuterium will be the intermolecular isotope effect.

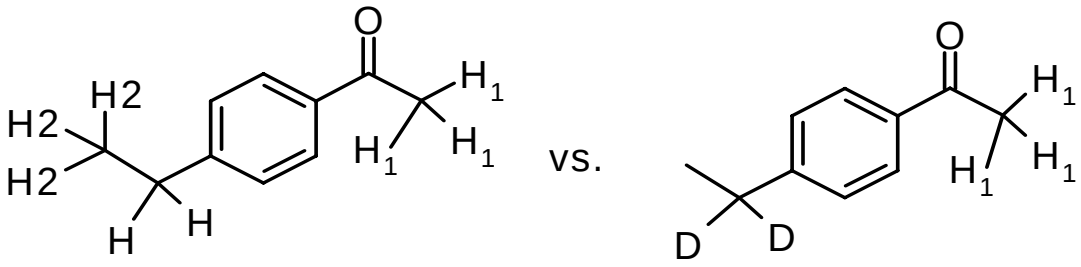


Figure 4. Hydrogens to be used to calculate intermolecular KIE.

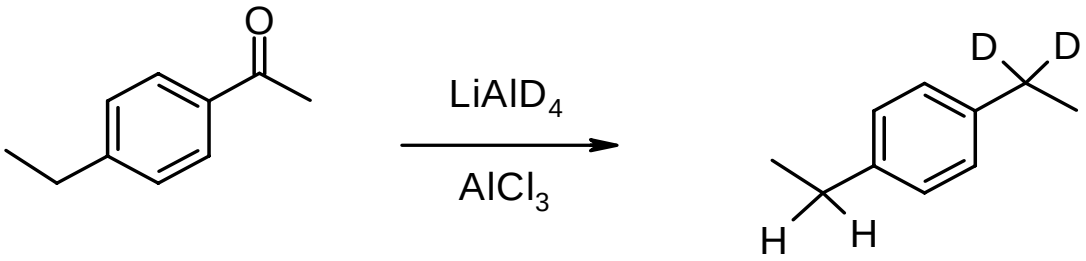
The isotope effects will be calculated using a comparison of the starting material versus

$$\frac{Non-deuteratedstarting \,/\, Deuteratedstarting}{H1\,\mathrm{Pr}\,oduct \,/\, H2\,\mathrm{Pr}\,oduct} \qquad \text{Equation (3)}$$

the product. The starting material ratio comes from the assumes ratio of hydrogen in the H2 position which for our starting material is 1 times the ratio of the actual of the deuterated and non-deuterated starting material. The final ratio is the amount of H1 vs the H2 Hydrogens H1 and H2 are shown in Fig 4. These numbers are plugged into Eq (3) resulting in the isotope effect.

The intramolecular isotope effect is found by using the following starting material made as shown in Scheme 5.

Scheme 5.



The intramolecular isotope effect is calculated by the ratio of the hydrogens in the H_1 and H_2 positions as shown in Fig 5.

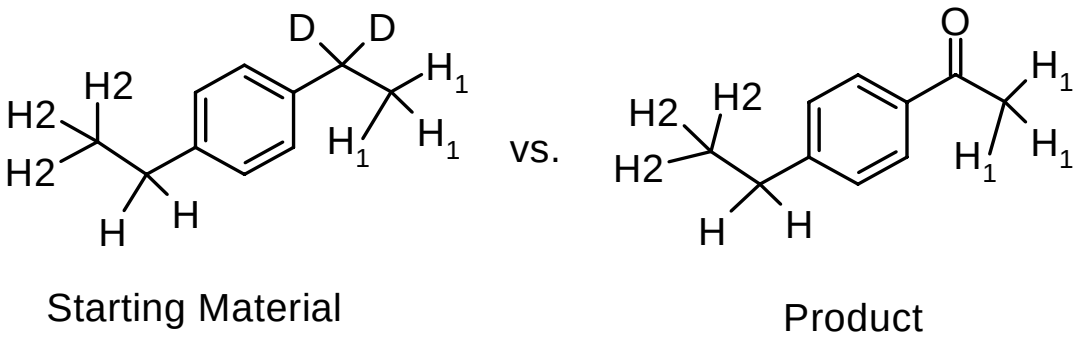


Figure 5. Hydrogens to be used to calculate intramolecular KIE.

The starting ratio can be assumed to be 1 because there by default has to be the same number of H_1 and H_2. The kinetic isotope effect is then calculated by equation 3.

$$\frac{H1starting \,/\, H2starting}{H1\,\mathrm{Pr}oduct \,/\, H2\,\mathrm{Pr}oduct} \qquad \text{Equation (4)}$$

Running the Gif chemistry for this study was not an easy task. This was expressed also by Perkins in his paper in the fact that his group had trouble reproducing the results of several of the Gif chemistry reactions[4]. He felt that the physical procedure could easily account for differences of results from one lab to another. The initial study undertaken had been to use an older version of the Gif chemistry. This version alternated addition of air and sulfur dioxide to afford the catalytic oxidation. These conditions were dangerous and presented many difficulties in that the gases were to be alternated at approximately an hour at a time but the conversion was slow enough that it took on the order of days to get the reaction to move forward and in the end this was deemed to be a more difficult path to take. It was then decided to use the Gif^{IV} conditions. This while

taking also on the order of days was a simpler procedure in which pure oxygen was kept in the headspace of the reaction vessel by use of a balloon.

The final purification of the product for NMR analysis also presented difficulties. The initial extrations which were purified first using simple distillation procedures. When initial analysis indicated further purification was needed the liquid was run through a preparatory GC in batches which were collected. This solution also had some minor impurities which inhibited analaysis. Since the product to be analyzed was a ketone it was decided that by reacting the product with 2,4-dinitophenylhydrazine only the ketone product would be collected and the impurities easily removed through washing the solid crystals collected. This transformation overcame the purification difficulties without changing any of the hydrogens to be quantified for the calculation of the kinetic isotope effect.

CHAPTER IV

EXPERIMENTAL

Synthesis of d_2-diethylbenzene

To 50 mL of diethyl ether in a N_2 charged well dried flask was added 3g of $LiAlD_4$ and 6 g of $AlCl_3$ was added in portions allowing solution to cool between each addition. A mixture of 20 g of 4-ethyl acetophenone in 100 mL of ether was added dropwise over 10 min. The reaction was then allowed to stir for 1 h. The reaction was then quenched by the slow addition of 10 mL of water, then by the addition of 10 mL of NaOH (0.2 M), and finally 30 mL of water. The mixture was then extracted 3x with 50 mL of ether. The extracts were combined and dried with $MgSO_4$ and distilled at 1 atm pressure. The resulting liquid was then distilled under vac to afford approximately 16g of d_2-diethyl benzene.

Sythesis of d_4-diethyl benzene

To 50 mL of diethyl ether in a N_2 charged well dried flask was added 6g of $LiAlD_4$ and 6 g of $AlCl_3$ was added in portions allowing solution to cool between each addition. A mixture of 20 g of 1,4-diacetylbenzene in 100 mL of ether was added dropwise over 10 min. The reaction was then allowed to stir for 1 h. The reaction was then quenched by the slow addition of 10 mL of water, then by the addition of 10 mL of NaOH (0.2 M),

and finally 30 mL of water. The mixture was then extracted 3x with 30 mL of ether. The extracts were combined and dried with $MgSO_4$ and distilled at 1 atm pressure. The resulting liquid was then distilled under vac to afford approximately 15 g of d_4-diethyl benzene.

Intramolecular KIE's

To 28 ml of pyridine was added 3 mL of water and 2.8 mL of acetic acid. To this solution was added 0.5 g of $FeCl_3$, and 0.25 g of Zinc powder. An amount of 1g of biphenyl was added as an internal standard. The solution was allowed to stir for about 15 min and then 1g of d_2-diethyl benzene was added. After which a portion was taken to establish a starting ratio of internal standard to diethylbenzene. The mouth of the flask was covered with a balloon filled with O_2 and left to stir for 5-7 days adding more O_2 to the balloon as needed. The percent conversion of the reaction was checked on portions until the reaction was to at least 20% conversion at which time the reaction was washed with 30 mL of water and extracted with 2x with 30 mL of ether with ml of diethyl ether washed again with 30 ml water followed by washing 2x with 30 ml of 3 M HCl. The majority of the ether was removed by rotatory distillation. The remaining ether was removed using simple distillation. This mostly purified liquid was then run through a preparatory GC in several small batches with the p-ethyl acetophenone product being collected. To the collected liquid was added 1 mL of a 2,4-dinitrophenylhydrazine solution and the remaining solution was filtered and washed with 4 mL of ice cold

ethanol. The crystals were dried under vac and then dissolved in $CDCl_3$. An NMR was aquired on an Inova 500 spectrometer at 500 MHZ.

Intermolecular KIE's

To 28 ml of pyridine was added 3 mL of water and 2.8 mL of acetic acid. To this solution was added 0.5g of $FeCl_3$, and 0.25 g of Zinc powder. An amount of 1g of biphenyl was added as an internal standard. The solution was allowed to stir for about 15 min and then 0.5g of d_4-diethyl benzene and 0.5g of non-deuterated diethyl benzene was added. After which a portion was taken to establish a starting ratio of internal standard to diethylbenzene. The mouth of the flask was covered with a balloon filled with O_2 and left to stir for 5-7 days adding more O_2 to the balloon as needed. The percent conversion of the reaction was checked on portions until the reaction was to at least 20% conversion at which time the reaction was washed with 30 mL of water and extracted with 2x with 30mL of diethyl ether washed again with 30 ml water followed by washing 2x with 30 ml of 3 M HCl. The majority of the ether was removed by rotatory distillation. The remaining ether was removed using simple distillation. This mostly purified liquid was then run through a preparatory GC in several small batches with the p-ethyl acetophenone product being collected. To the collected liquid was added 1 mL of a 2,4-dinitrophenylhydrazine solution and the remaining solution was filtered and washed with 4 mL of ice cold ethanol. The crystals were dried under vac

and then dissolved in $CDCl_3$. An NMR was aquired on an Inova 500 spectrometer at 500 MHZ.

CHAPTER IV

DISCUSSION AND CONCLUSION

Results

Running the Gif chemistry for this study was not an easy task. This was expressed also by Perkins in his paper in the fact that his group had trouble reproducing the results of several of the Gif chemistry reactions. He felt that the physical procedure could easily account for differences of results from one lab to another. The initial study undertaken had been to use an older version of the Gif chemistry. This version alternated addition of air and sulfur dioxide to afford the catalytic oxidation. These conditions were dangerous and presented many difficulties in that the gases were to be alternated at approximately an hour at a time but the conversion was slow enough that it took on the order of days to get the reaction to move forward and in the end this was deemed to be a more difficult path to take. It was then decided to use the Gif^{IV} conditions. This while taking also on the order of days was a simpler procedure in which pure oxygen was kept in the headspace of the reaction vessel by use of a balloon.

The final purification of the product for NMR analysis also presented difficulties. The initial extrations which were purified first using simple distillation procedures. When initial analysis indicated further purification was needed the liquid was run through a preparatory GC in batches which were collected. This solution also had some minor impurities which inhibited analaysis. Since the product to be analyzed was a ketone it

was decided that by reacting the product with 2,4-dinitophenylhydrazine only the ketone product would be collected and the impurities easily removed through washing the solid crystals collected. This transformation overcame the purification difficulties without changing any of the hydrogens to be quantified for the calculation of the kinetic isotope effect.

The reactions were performed over a 5-7 period during which the conversion was monitored by comparing the starting material concentration vs an internal standard biphenyl which was added at the start of the reaction by removing small aliquots and quantifying by GC. When the reaction reached approximately 20-25% the reaction mixture was extracted with diethyl ether and the product subsequently purified as mentioned above. The product was then analyzed by NMR with the key hydrogens quantified and then plugged into the corresponding equation for either the inter or intramolecular isotope effect.

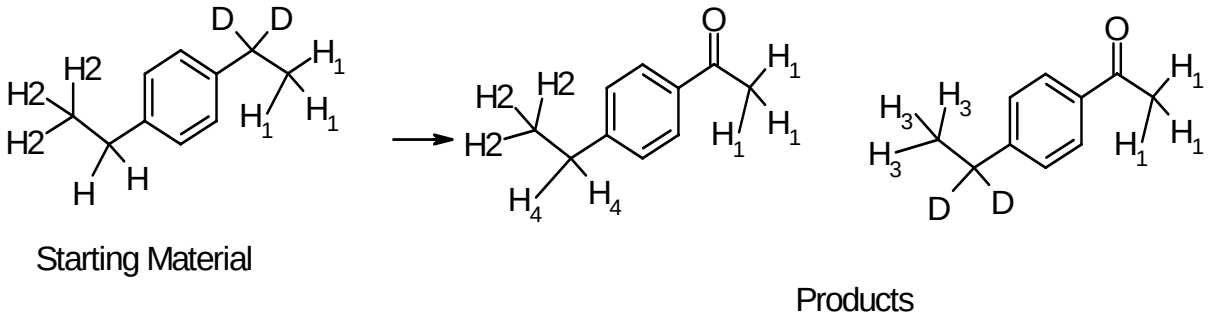


Figure 6. The hydrogens measured.

From Fig 6 this is seen as a quantification of H_1 and H_2 in the product. The use of H_1 is such that it encompasses the product derived from either the reaction of the hydrogen or

the deuterium and while they are different in the starting material the transformation does not depend on whether they derived from the starting H_1 or H_2. For the product analysis it would be possible to use either H_2 or H_4.

The results for the Intra and Intermolecular isotope effects are shown the Fig 7

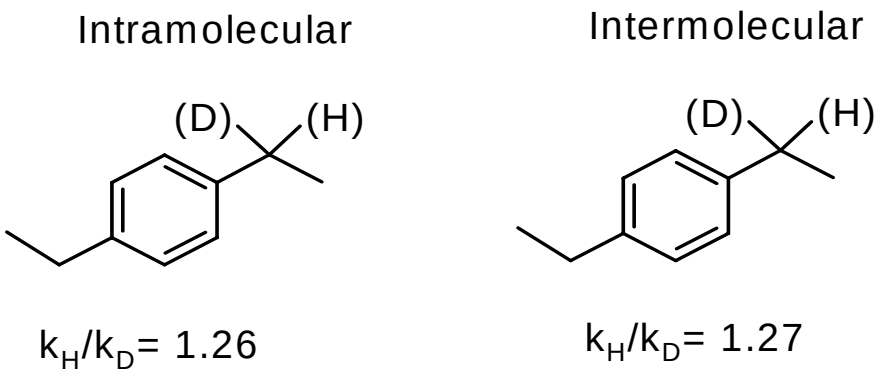


Figure 7. The measured KIEs.

This shows that the inter and intramolecular isotope effects are not different. The difference is within the limits of error on this method.

Discussion

The results show that the inter and intramolecular isotope effects are very similar. This would suggest that the true bond breaking isotope effect is in fact 1.27. This is consistent with the "modest kinetic isotope effects" reported by other labs[4]. This is

consistent with other radical mechanism involving hydroxyl radical and yet another piece of evidence to say that the Fe^{V} superoxide insertion mechanism is incorrect.

This is similar but with different results to a study undertaken on Methane Monooxygenase. The original kinetic isotope effects measured were very modest and were counter to what was expected for a metal insertion into a carbon hydrogen bond. When the intramolecular isotope effect was measured however it showed a much higher kinetic isotope effect. This was taken as evidence that indeed the diffusion into and out of the active site of the enzyme was dominating the overall reaction but when the intramolecular isotope effect was measured the chemically important steps showed that the true chemical transition state kinetics were in line with the proposed metal insertion of a carbon hydrogen bond[4].

This would also suggest that while Newcombe's conclusion that is indeed a radical mechanism the conclusion that it is also a diffusion limited mechanism is flawed. The lack of a difference in the inter and intramolecular kinetic isotope effects leads to the conclusion that there are no other barriers in the mechanism that are higher than the radical hydrogen abstraction.

REFERENCES

1. Barton, D. H. R. *Synlett*. **1997**, 229.
2. Barton, D.H.R.; Doller, D.; Geletii, Y.V., *Tetrahedron Letters,***1991**, *31*, 3811.
3. Barton , D.H.R.; Halley, F.; Ozbalik, N.; Schmidt, M.; Young, E.; Balavoine, G., *J. Am. Chem. Soc.* **1989**, *111***,** 7144.
4. Perkins, M. J., *Chemical Society Reviews*, **1996**, *25***,** 229.
5. Barton,D.H.R.; Doller, D.; Beviere, S.D., *Tetrahedron Letters*, **1991**, 36, 4671.
6. Barton, D.H.R.; Doller, D.; Geletii, Y.V., *Tetrahedron Letters,***1991**, *32*, 4671.
7. Barton, D.H.R.; Li, Tingshen, *Chemical Communications*, **1998**, *7*, 821.
8. Barton, D.H.R.; Ceshing, S.; Sobkowiak, A.; Zhang, L.; Ozbalik N.; Sawyer, D.T., *J. Am. Chem. Soc.* **1989**, *111*, 8030.
9. Newcombe, M.; Simakov, P.A.; Park, Seung-Un, *Tetrahedron Letters*, **1996**, *37***,** 819.
10. Gozzo, F., *Journal of Molecular Catalysis A: Chemical*, **2001**, *194***,** 1.

VITA

Name:	Joshua G. Wagner
Address:	3815 Ashwood Cir La Porte, TX 77571
Email Address:	wags692@yahoo.com
Education:	B.S., Chemistry, Villa Julie College , 1999 M.S., Organic Chemistry, Texas A&M University, 2009